

# Advances in understanding and treating dystrophic epidermolysis bullosa

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## Abstract

Epidermolysis bullosa is a group of inherited disorders that can be both systemic and life-threatening. Standard treatments for the most severe forms of this disorder, typically limited to palliative care, are ineffective in reducing the morbidity and mortality due to complications of the disease. Emerging therapies—such as the use of allogeneic cellular therapy, gene therapy, and protein therapy—have all shown promise, but it is likely that several approaches will need to be combined to realize a cure. For recessive dystrophic epidermolysis bullosa, each particular therapeutic approach has added to our understanding of type VII collagen (C7) function and the basic biology surrounding the disease. The efficacy of these therapies and the mechanisms by which they function also give us insight into developing future strategies for treating this and other extracellular matrix disorders.

"The outcome of any serious research can only be to make two questions grow where only one grew before."  
Thorstein Veblen, *The Evolution of the Scientific Point of View*, 1908.

## Born to blister

Recessive dystrophic epidermolysis bullosa (RDEB) is a severe inherited skin disorder characterized by chronic skin blistering, diminished wound healing, joint contractures, esophageal strictures, pseudosyndactyly, corneal abrasions, and a shortened life span [1-3]. Affected individuals suffer through intense pain throughout their lives, with few or no effective treatments available to reduce the severity of their symptoms. Along with the life-threatening infectious complications associated with this disorder, many individuals will develop an aggressive form of squamous cell carcinoma [4,5].

RDEB is caused by mutations in *COL7A1*, the gene that encodes for C7 [6,7]. One of the most severe types of epidermolysis bullosa, RDEB is typically inherited in an autosomal-recessive fashion. It results from transfer of

the mutated *COL7A1* copies from both parents, who carry the mutation, to the affected offspring [8]. C7 is the main component of anchoring fibrils, structures that attach the dermis to the epidermis at the dermal-epidermal junction [9-11]. The inability of these anchoring fibrils to form and function properly causes the epidermis to not adhere to the underlying dermis [12]. This loss of structural integrity causes the skin to become susceptible to even slight trauma and also hinders the skin from healing productively [13,14]. It is likely that the constant cellular stress from the skin trying to heal itself, along with the resulting chronic inflammation, is the main reason for the increased risk of squamous cell carcinoma in individuals with RDEB [5,15-17].

Owing to its nature and severity, RDEB presents unique challenges for developing successful therapies that simultaneously alleviate the plethora of complications while having a significant impact on survival and quality of life. Recent approaches such as allogeneic cellular therapy, gene therapy, and protein therapy [18-23] show

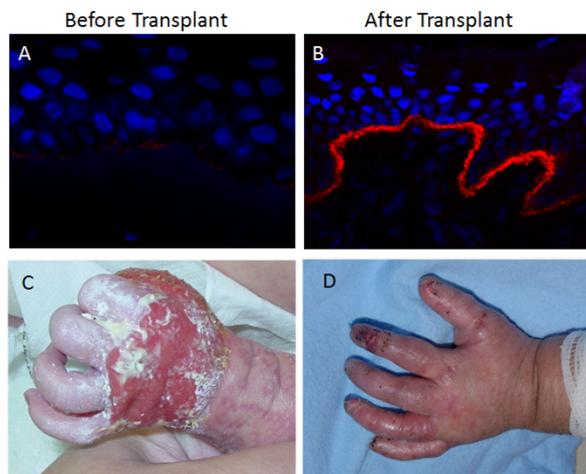
promise. Beyond the potential translational benefit of these studies, they have also significantly advanced our understanding of the biological properties of skin. Armed with this information and the recent technical advances, we believe the collective ability of multiple teams around the globe to both understand and treat RDEB is approaching a pivotal point in achieving effective, sustainable treatment options.

### **Allogeneic cellular therapies: from bench to bedside**

Initial studies using allogeneic cells for the *in situ* treatment of epidermolysis bullosa included allogeneic fibroblasts [24-27] and mesenchymal stromal cells [28] and gene-corrected autologous epidermal stem cells [29]. These early studies using donor cells for local skin repair were crucial in demonstrating the capacity of allogeneic cells to correct this extracellular matrix disorder, but the benefits were limited to the site of application. Although the pathology of severe generalized RDEB is most apparent in the skin, its effects are numerous and systemic, and any therapy to treat the systemic manifestations requires broad delivery of C7 throughout the body. The prototype of cell therapy for genetic disorders is hematopoietic cell transplantation (HCT), which allows systemic and long-term distribution of donor cells in the recipient [30,31]. There is a growing amount of evidence describing the participation of cells with hematopoietic origin that are responsible for orchestrating and contributing to productive wound healing [32-35]. The process of wound healing in injured skin is complex, and a wide variety of cells from the bone marrow are recruited and participate in regulating inflammation, re-epithelialization, and extracellular matrix production [35].

Initial studies investigating the potential for bone marrow cells to treat extracellular matrix disorders confirmed this potential [36,37]. In a mouse transplantation model of RDEB, purified populations from the wildtype bone marrow were shown to home to injured skin and secrete C7 [37]. In turn, this improved the blistering phenotype and increased survival rates in treated mice. This approach was also shown to be effective in treating other forms of epidermolysis bullosa [38]. These studies provided the proof of principle needed for the first clinical trial using HCT to treat RDEB. The results from the initial patients enrolled in the clinical trial demonstrated the efficacy of HCTs and also revealed new information about how the bone marrow contributes to wound healing [18]. The patients treated with HCT not only displayed an increase in C7 deposition (Figure 1) but also showed a substantial level of donor chimerism in the skin following transplant. Exactly which cell types are responsible for homing to the skin, producing C7, and

**Figure 1. Increase in type VII collagen (C7) deposition and improvement of clinical symptoms after hematopoietic cell transplantation (HCT) treatment for recessive dystrophic epidermolysis bullosa (RDEB)**



Immunofluorescent stain of C7 (red) and 4'-6-diamidino-2-phenylindole (DAPI) (blue) visualizing the dermal-epidermal junction (**A**) before transplant and (**B**) 2.5 years after transplant. Photos of an RDEB patient presenting wounds over the back of the hand (**C**) before transplant and (**D**) the improvement after transplant.

contributing to high levels of donor chimerism is still being determined, but several studies of this phenomenon have uncovered potentially relevant mechanisms. For example, a recent study described a particular subset of bone marrow cells expressing the surface marker platelet-derived growth factor receptor alpha that respond to a homing signal in injured skin, high-mobility group box (HMGB1) [39]. This subset was shown to produce C7 in the transplanted mouse model of RDEB. Other studies have demonstrated that certain subsets of bone marrow or cord blood cells were capable of producing C7 and that production increased in the context of wound healing [35,40]. Although it remains to be seen whether this subset of cells can be enriched prior to transplant or whether particular homing signals can be manipulated in order to improve transplant efficacy, these findings improve our understanding of how HCT can treat extracellular matrix disorders [41-43].

### **Induced pluripotent stem cells: evidence-based approaches**

Along with HCT, another option for future therapies in RDEB would be the use of cells derived from personalized induced pluripotent stem (iPS) cells [44-46]. In principle, iPS cells offer an inexhaustible supply of cells capable of differentiating into almost all cell types of the body.

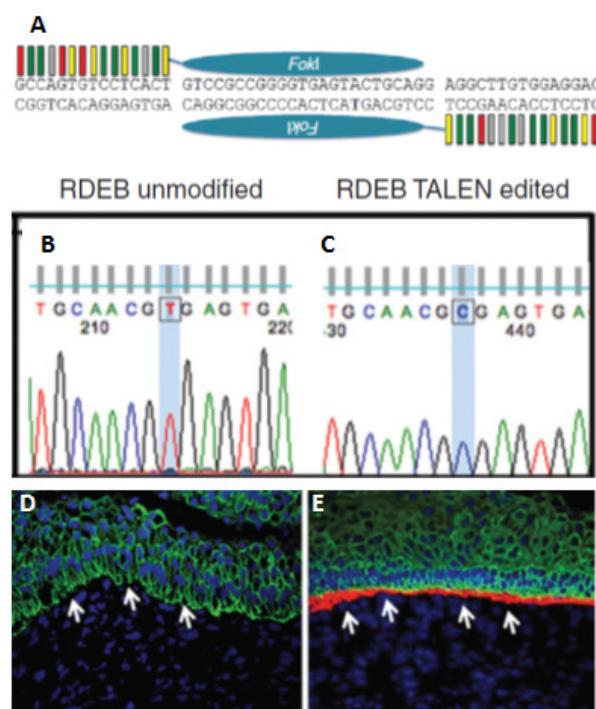
They have already been used in *ex vivo* modelling of many genetic diseases [47-49]. Skin cells isolated from both patients with RDEB and patients who suffer from the closely related disorder, junctional epidermolysis bullosa (JEB), can be reprogrammed into iPS cells that can be used to investigate the mechanisms of mucocutaneous destruction and wound healing in disorders with deficiencies in the protein complexes that support structural integrity of the epidermis and extracellular matrix of the dermis [50,51]. Furthermore, keratinocytes isolated from a healthy patch of skin from a patient with RDEB were reprogrammed into iPS cells [52]. The healthy patch of skin was determined to be a result of somatic mosaicism [53-55], and iPS cells derived from this healthy patch produced functional, biologically relevant levels of C7. These cells, and similar cells derived from mosaic patches in JEB individuals [56-58], represent a serendipitous opportunity for therapeutic use and a spearhead for the future of autologous cellular therapy [59]. RDEB iPS cells can also be differentiated into keratinocytes and fibroblasts, the two cell types that produce C7 in the skin, and can be used to construct full-thickness three-dimensional skin equivalents [60-62]. Fibroblasts, keratinocytes, and skin equivalents produced from iPS cells could be used therapeutically to treat localized, topical wounds. In addition to differentiation into skin cells and reconstruction of epidermis and dermis, recent studies showed that RDEB iPS cells can generate cells with surface markers similar to those expressed by human hematopoietic cells [63]. Intense efforts are under way to derive transplantable human iPS cell-derived hematopoietic stem cells that can be used for HCT [64-70]. These advances, along with the allogeneic HCT being used today, are the first steps needed in developing a more comprehensive therapy for RDEB. Other simultaneous advances in genome engineering should eventually allow a patient's own cells to be gene-corrected and then reprogrammed into iPS cells for use in autologous therapy.

### Gene therapy: both inside and outside of the COL7A1 locus

Although allogeneic HCT is the most effective and widespread cellular therapy of genetic disorders to date, it requires a human leucocyte antigen-matched donor, and the HCT process itself can be life-threatening [71-75]. Autologous transplant would be a preferred option. Multiple approaches have been used for correcting *COL7A1*, including retroviral vectors, self-inactivating retroviral or lentiviral vectors, and retroviral vectors encoding a 3' pre-trans-splicing molecule [19,76-78]. These approaches demonstrated that transduced cells were capable of producing functional and biologically significant levels of C7. Although viral-mediated transgenesis is an efficient way of correcting a genetic defect in

patients' cells [79-83], correcting the endogenous mutation *in situ* in the genome could offer benefits over the use of viral vectors. Endogenous correction ensures physiological transcriptional control of *COL7A1* and expression at biologically appropriate levels and—because the transgene is designed to not integrate in the host genome—reduces off-target, potentially oncogenic events caused by random insertional mutagenesis. Recently, genome-editing strategies using zinc-finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs) have demonstrated the ability to target specific sites in the human genome and correct endogenous mutations [84-87]. TALENs have been used successfully in combination with homology-directed repair to correct the *COL7A1* mutation in human fibroblasts from patients with RDEB (Figure 2) [87]. These corrected fibroblasts were capable of producing wildtype C7 with minimal off-target genomic effects. Moreover, these cells could be reprogrammed into

**Figure 2. Using transcription activator-like effector nucleases (TALENs) to genetically correct mutation in *COL7A1* gene leads to phenotypic correction**



**(A)** Diagram of TALEN targeting *COL7A1* mutation g.1837 C>T, which leads to a premature stop codon. Sequence analysis of base pair 1837 from **(B)** recessive dystrophic epidermolysis bullosa (RDEB) fibroblasts and **(C)** the corresponding TALEN-corrected fibroblasts. Immunofluorescent staining of type VII collagen in **(D)** skin-like structures formed from RDEB-induced pluripotent stem (RDEB-iPS) cells and **(E)** the corresponding TALEN-corrected iPS cells.

iPS cells and, when xenotransplanted into immunodeficient mice, generated human skin-like structures with apparently normal C7 deposition. These data support the possibility that *in situ* correction of the COL7A1 locus leads to physiological C7 production and could offer therapeutic benefit to individuals with RDEB. Although TALEN correction appears to be a superior option to previous gene therapy methods, TALEN construction must be tailored to the particular COL7A1 loci that harbor the specific RDEB mutations, which can be both costly and labor-intensive [88]. As there are hundreds of causative mutations for RDEB characterized to date, using this approach on a larger scale may be challenging [89]. With the advent of clustered regulatory interspaced short palindromic repeats and associated proteins (CRISPR/Cas), the ability to correct multiple genetic mutations in human cells might have become considerably easier [90-92], although their off-target profile needs to be carefully analyzed [93].

### **Protein therapy: translation of basic scientific insights**

Protein therapy has been used for other inherited disorders of enzyme production due to the inherent capacity of affected cells to take up the missing enzyme [94,95]. Using protein therapy to treat inherited defects of structural protein production has been limited in comparison, but recent studies have demonstrated exciting results, specifically in using C7 protein therapy in pre-clinical models of RDEB [96,97]. Intradermal injections of C7 resulted in the stable incorporation of recombinant C7 into the basement membrane zone and corrected the phenotype in a murine model of RDEB. Intravenous injection of recombinant C7 into RDEB mice resulted in systemic biodistribution and deposition of C7 in wounded skin, but not in unaffected skin sites and internal organs [20]. It is likely that the soluble nature of C7 (unlike other collagens that aggregate and collect in the bloodstream) underlies both the safety and efficacy of systemic C7 infusion [98]. In addition, topical C7 application not only improves the phenotype in an RDEB murine model but may accelerate wound healing in skin that produces functional C7 as well [21]. Thus, the ability of C7 to promote healing in normal skin highlights its importance in coordinating cell migration and extracellular matrix organization in skin repair [13]. The necessary dosing levels and repeated applications of using recombinant C7 for RDEB patients has yet to be determined, although the initial pre-clinical studies have shown promising results with levels that should be attainable for clinical settings.

### **Future: finding a cure for the incurable**

The future of medicine, including the quest to decrease suffering in individuals with RDEB, will involve a

nuanced understanding of mechanisms underlying patient-specific therapies and combinatorial approaches to achieve the best possible outcomes. Although cellular therapies have been effective in ameliorating the severe generalized phenotype of RDEB, additional modifications, including local application of recombinant homing signals (such as HMGB1) or topical C7 therapy to remaining wounds, will likely complement the use of systemic cellular therapy. Also, inclusion of multiple cell types, such as hematopoietic stem/progenitor cells, mesenchymal stromal cells, fibroblasts, or keratinocytes, alone or after HCT, may speed and enhance wound healing. Local administration will be required in sites where systemic cell therapy offers little benefit, such as in the eyes, where limbal cell transplantation has been shown to be effective in treating other types of corneal disorders or trauma [3,99-101].

Certain aspects about why particular therapies are effective at treating RDEB are unknown, but findings from one therapy can give clues to questions that remain about another. For instance, the finding that intravenous injection of recombinant C7 results in C7 deposition at the dermal-epidermal junction of injured skin may have implications regarding the mechanisms of HCT for treating RDEB. It is conceivable that cells are not required to be in close proximity to the dermal-epidermal junction in order to produce the C7 that is deposited there. Rather, owing to the soluble nature of C7, cells from the graft could produce C7 in another site (such as the bone marrow), which is then taken up by the bloodstream and distributed systemically to injured skin. Thus, the beneficial effects of donor cells that are present near the dermal-epidermal junction following HCT can be amplified by these distant C7-producing cells. It has also been hypothesized that donor cells, such as those used in allogeneic fibroblast therapies, may not only be producing their own functional C7 but inducing recipient keratinocytes and fibroblasts to produce increased levels of mutant C7 as well, through induction via heparin-binding epidermal growth factor-like growth factor signaling [102]. Investigating such possibilities may help discover or define new roles for cell types or signals that were not previously known to be important for wound healing or extracellular matrix production in RDEB, other genodermatoses, and acquired skin disorders and injuries.

Along with new discoveries, critical information will become available following the treatment of these patients. Whether the new approaches are deemed successful will not only be evaluated by the long-term improvement of their daily lives but also by the reduction of the associated risks of RDEB, including squamous cell carcinoma and systemic infections.

Integrating treatments for these complications will be necessary moving forward, as will expanding the use of novel therapies to more complicated cases. It also remains to be seen whether patients treated with cellular, genetic, or protein therapies develop an acquired immune response to antigens derived from the newly synthesized C7 that was not present before therapy, similar to the related autoimmune disorder epidermolysis bullosa acquisita [103-105]. No anti-C7 antibodies were detected initially in patients who received bone marrow transplant, but the long-term results remain to be determined [18]. In the case of HCT, reduced intensity conditioning and using alternative sources of hematopoietic cells may help improve survival rates and lessen the associated risks, such as graft-versus-host disease and infections. Further improvements and adjustments to these novel approaches will hopefully be made.

## Abbreviations

C7, type VII collagen; HCT, hematopoietic cell transplantation; iPS, induced pluripotent stem (cell); JEB, junctional epidermolysis bullosa; RDEB, recessive dystrophic epidermolysis bullosa; TALEN, transcription activator-like effector nuclease.

## Disclosures

The authors declare that they have no disclosures.

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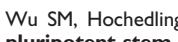
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